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# High versus low dialysate sodium: a single-center small-scale prospective study

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## ABSTRACT

**Aims:** The matter of dialysate sodium concentration has become progressively substantial in the last 50 years, when dialysis modalities have advanced quickly. In many studies, it has been established that dialysate sodium value is correlated with blood pressure alternance, hypervolemia, interdialytic weight gain (IDWG), and chronic inflammation. However, there is no clear knowledge about its direct effect on inflammation. In this study, we profited from high-sensitivity C-reactive protein (hs-CRP), which is a helpful marker, to survey the inflammation correlation with dialysate sodium (DNa).

**Methods:** 109 non-diabetic hemodialysis patients were enrolled in the study. All patients participating in the study were new onset, less than 6 months dialysis patients and met Kt/V of 1.4 at minimum criteria.

**Results:** They were divided into two groups: group 1, low dialysate sodium (137 mmol/L) and group 2, conventional dialysate sodium (140 mmol/L) and followed-up for two months. During the follow-up period, serum hs-CRP levels were measured and categorized as baseline, 1st month and second month level.

**Conclusion:** As a result, no statistically remarkable disparity between the groups were determined in terms of serum hs-CRP levels at baseline, 1st month, and 2nd month of the study ($p>0.05$). We did not establish any significant differences that would make it worth ignoring some symptoms symptoms such as cramps and hypotension.

**Keywords:** Chronic kidney disease, hemodialysis, dialysate sodium, chronic inflammation, high-sensitivity CRP

## INTRODUCTION

The most critical function of the kidneys is to maintain homeostasis. They exert this by supplying acid-base, water, sodium, and other electrolyte equilibrium, and by removing toxins meanwhile. The kidneys are in charge of the generation of vital enzymes and hormones. One of the tools used to provide hemostasis is a hemodialysis device for chronic kidney end stage patients.

While preserving a relatively stable plasma concentration, the dialysis machine takes out the sodium and water assembled over the interdialytic break. The major exogenous source of sodium is dietary, and the minor source could be dialysate sodium. DNa formulas have developed over the past 50 years. Higher dialysate sodium concentrations take the lead of hemodynamic stabilization and diminish intradialytic findings but aggravate thirst and unavoidable volume expansion of course. On the contrary, lower DNa may cause less thirst and this provides more controlled weight gain but unfortunately it concludes with a greater hemodynamic instability. Observational data recommend that the correlation between dialysate sodium and consequences may vary according to serum sodium levels, sustaining the individuality of dialysate sodium.[1]

In chronic kidney disease (CKD) patients, uremia triggered chronic systemic inflammation, and this led to the 10-to 20-fold higher mortality than that in the healthy people.[2,3] Inflammation is highly common in HD patients and undesirable outcomes such as malnutrition, anemia, accelerated vascular disease occur consequently.[4,5]

Conventional factors such as diabetes, hypertension, sedentary lifestyle, lipid disorder and hyperhomocysteinemia, hyperparathyroidism, volume overload are significant causes of inflammation. In recent research, fluid overload has been related with an inflammatory reaction.[6] Takahashi's study demonstrated that monocyte IL-6 mRNA deliverance and augmentation of IL-6 levels are associated with volume overload in hemodialysis and peritoneal dialysis patients.

This can also be clarified by the hypervolemia that brighten inflammation by the translocation of endotoxins from the edematous intestinal loops; however, previous studies have argued that salt itself may incite $T_H17$ immunity in vivo through effects on the gut microbiota.[7] The decrease of dialysate sodium from 140 to 137 mEq/L was came along with a prominent amelioration in endothelial injury, hemodynamics, and oxidative state.[8,9]

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Therefore, in the last 50 years, dialysate sodium prescriptions have been tried to be continuously improved. However, the deficiency of randomized controlled clinical trial data in this area has embarrassed the improvement of open clinical guidelines regarding the ideal touch for dialysate sodium prescription.

It is unclear whether low sodium in dialysis fluid make better overall health and well-being for people on hemodialysis, since there is an interference of probably helpful and distorted effects, and available research studies were not designed to learn about impacts of the intervention on the heart or on overall patient health.[10]

With this intention, we conducted a prospective controlled study in our hemodialysis clinic via serum hs-CRP measurement and observed the effects of both conventional dialysate and low sodium dialysate on chronic inflammation. In this study, we aimed to determine the optimum DNa value to decrease inflammation considering current information.

## METHODS

The study was conducted with the permission of the Ethics Committee of University of Health Sciences Trabzon Kanuni Training and Research Hospital (Date: 17.02.2017, Decision No: 23618724-000-2294). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this prospective controlled research, our goal is to investigate whether or not lower dialysate sodium decreases inflammatory status of the body. 109 hemodialysis patients were enrolled in University of Health Sciences Kanuni Training and Research Hospital between May-July 2017. The exclusion criteria were using of hemodiafiltration for HD, being under 18 years, having active or chronic inflammatory diseases, diabetes, hypertension and more than 3 times per week hemodialysis frequency. In addition, none of the participants were taking any medications that could play a role in sodium metabolism.

All patients were in dialysis with arteriovenous fistula less than 6 months and met Kt/V of 1.4 at minimum criteria. The ratio Kt/V (K is patient clearance, t dialysis time, V urea space) was calculated by Kt/V dialysis dose Daugirdas formula based on standard bicarbonate 4 hours dialysis session. (KtV Daugirdas=-ln ((BUNPost/BUNPre)-(0.008*hour))+((4 -(3.5*BUNPost/BUNPre))*UFVol/weight).

Pre-dialytic body temperatures were also measured in every dialysis session and temperature outside of 36.5-37.5 degrees were excluded.

The primary endpoint was determined as feeling of thirst or xerostomia, dietary sodium intake, cramping and intradialytic hypotension. Patients were randomly allocated into two groups: group 1, low dialysate sodium (137 mmol/L), and group 2, conventional dialysate sodium (140 mmol/L) and followed up for 2 months. The study groups were not blinded. After the patients were divided into two groups, serum hs-CRP levels were measured at the beginning of the study and at the 1st and 2nd month of dialysis therapy.

### Statistical Analysis

The main outcome was serum hs-CRP level, which was measured with a human high-sensitivity protein Elisa Kit. Statistical analysis program was the NCSS 2007.

## RESULTS

According to groups, there was no statistically important distinction between the ages (p>0.05). The rate of female cases in group 2 was higher than that of male cases (p=0.010; p<0.05) (**Table 1**).

In group 1, there was not any remarkable difference of hs-CRP level at the 1st and 2nd month compared to the beginning of the treatment (p>0.05) (**Table 2**).

In group 2, we found the similar result. Hs-CRP levels did not indicate any prominent variation during the study period. (p>0.05) (**Table 2**).

But most importantly, we could not determine any considerable difference between the groups in terms of hs-CRP (p>0.05) (**Table 3, Figure**).

During the study, intervention did not augment the episodes of cramping and intradialytic hypotension.

## DISCUSSION

By affecting 10–16% of the population, CKD is a progressively widespread condition admitted as a public health priority.[11] In accordance with diverse investigations, more than 50% of patients with CKD Stage 3 or higher possess high CRP level.[12,13]

Chronic inflammation in CKD owns multiple etiologic factors such as dialysis membranes, catheters, uremic toxins, sodium, and fluid overload. Chronic and persistent inflammation is thought to contribute to atherosclerosis, osteoporosis, diabetes, cancer, and depression in CKD. Therefore, uncontrolled inflammatory response is an important preventable parameter in these patients. However, the effect of DNa on chronic inflammation remains controversial.

When dialysis began in the 1940s, Willem Kolff adjust the DNa concentration to 126.5 mEq/L.[14]

By the 1960s, most dialysis center chose to set DNa to 130 mEq/L.[15] During the 1970s and 1980s DNa concentrations were thus augmented further to optimize intradialytic BP stability. By the 1980s, DNa concentration had been 135 mEq/L generally.[16]

A decade later, DNa had increased to 140 mEq/L which is the most common concentration today.[17]

We have already known that higher DNa prescription could cause significantly higher interdialytic weight gain (IDWG). Additionally, a low dialysate sodium was recommended for better control of chronic inflammation because of its advantageous effect on IDWG and volume overload control.[18]

It is certain that low DNa decreases IDWG and might support to improve endothelial damage and inflammation implicitly. But meanwhile low DNa can also increase the incidence of hypotensive episodes and muscle cramps.[19]

**Table 1.** Evaluation of demographic characteristics by groups

| | | Groups | | | Test values |
|---|---|---|---|---|---|
| | | **Total** | **Group 1 (n=56)** | **Group 2 (n=53)** | **p** |
| Age (year) | Min-max-(median) | 24-88 (65) | 24-88 (63) | 31-81 (66) | t:-0.559 |
| | Averages±SD | 61.94±13.13 | 61.25±14.09 | 62.66±12,12 | [a]0.577 |
| | | **n (%)** | **n (%)** | **n (%)** | |
| Gender | Female | 46 (42.2) | 17 (30.4) | 29 (54.7) | $\chi^2$:6.624 |
| | Male | 63 (57.8) | 39 (69.6) | 24 (45.3) | [b]0.010* |

[a]Student-t test, [b]Pearson Chi-square test, *p<0.05

**Table 2.** Evaluation of hsCRP measurements by groups at the beginning ,1st and 2nd month

| | | Groups | | | Test value |
|---|---|---|---|---|---|
| | | **Total** | **Group 1 (n=56)** | **Group 2 (n=53)** | **[c]p** |
| Beginning hs-CRP | Min-max (median) | 0.03-13.22 (0.50) | 0.03-13.22 (0.56) | 0.03-6.36 (0.46) | Z:-0.467 |
| | Averages±SD | 1.11±1.85 | 1.25±2.22 | 0.96±1.36 | 0.641 |
| 1. month hs-CRP | Min-max (median) | 0.05-11.49 (0.67) | 0.05-11.49 (0.51) | 0.09-5.30 (0.80) | Z:-0.785 |
| | Averages±SD | 1.30±1.82 | 1.41±2.24 | 1.18±1.24 | 0.432 |
| 2. month hs-CRP | Min-max (median) | 0.02-10.95 (0.66) | 0.06-10.95 (0.61) | 0.02-10.43 (0.75) | Z:-0.840 |
| | Averages±SD | 1.43±2.04 | 1.40±2.13 | 1.47±1.96 | 0.401 |
| Test value | | $\chi^2$:3.323 | $\chi^2$:0.893 | $\chi^2$:3.438 | |
| | [d]p | 0.190 | 0.640 | 0.179 | |
| Beginning-1. month | Difference | 0.20±2.13 | 0.17±2.56 | 0.23±1.57 | Z:-1.012 |
| | [c]p | 0.099 | 0.912 | 0.135 | 0.311 |
| Beginning-2. month | Difference | 0.33±2.30 | 0.15±2.52 | 0.52±2.04 | Z:-0.176 |
| | [c]p | 0.072 | 0.366 | 0.297 | 0.860 |
| 1.-2. month | Difference | 0.13±1.92 | -0.02±1.89 | 0.29±1.96 | Z:-0.443 |
| | [c]p | 1.000 | 1.000 | 1.000 | 0.658 |

[c]Mann-Whitney U test, [d]Friedman test, *p<0.05, [c]Bonferroni Correctedi Wilcoxon signed ranks test, 00000, hs-CRP: High-sensitivity C-reactive protein

**Table 3.** Beginning, 1st and 2nd month of hsCRP measurement evaluation according to groups

| | | Groups | | | Test value |
|---|---|---|---|---|---|
| | | **Total** | **Group 1 (n=56)** | **Group 2 (n=53)** | **[c]p** |
| Beginning hs-CRP | Normal (0-5) | 103 (94.5) | 52 (92.9) | 51 (96.2) | $\chi^2$: 0.594 |
| | High (≥5.1) | 6 (5.5) | 4 (7.1) | 2 (3.8) | [f]0.679 |
| 1st hs-CRP | Normal | 104 (95.4) | 52 (92.9) | 52 (98.1) | $\chi^2$:1.719 |
| | High | 5 (4.6) | 4 (7.1) | 1 (1.9) | [f]0.364 |
| 2nd hs-CRP | Normal | 103 (94.5) | 52 (92.9) | 51 (96.2) | $\chi^2$:0.594 |
| | High | 6 (5.5) | 4 (7.1) | 2 (3.8) | [f]0.679 |

[f]Fisher's Exact test, hs-CRP: High-sensitivity C-reactive protein

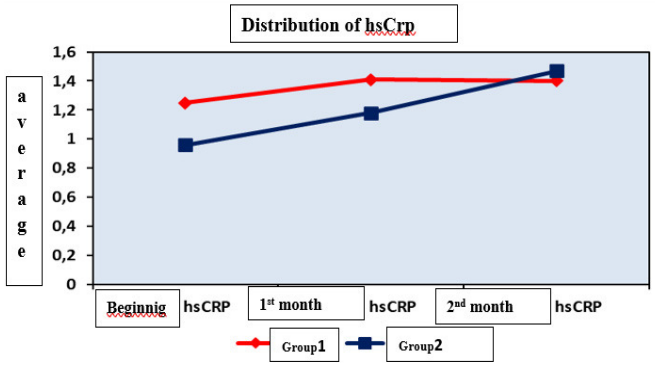


**Figure.** Distribution of hs-CRP
hs-CRP: High-sensitivity C-reactive protein

Mc Causland et al.[1] examined 2.272 patients from Satellite Healthcare and found that higher DNa concentrations (>140 mEq/L fixed or modeled vs. ≤140 mEq/L) were associated with greater mortality.

Hecking et al.[27] pointed that among all patients, higher DNa concentrations were not correlated with greater mortality but were associated with a lower risk of hospitalization (HR=0.97 per 2 mEq/L higher dialysate sodium, 95% CI 0.95–1.00, p=0.04). It is also reported that the risk of all-cause hospitalizations and hospitalizations due to fluid overload decreased by 3 and 6% per 2 mmol/L increase in DNa (hazard

ratio 0.97; 95% confidence interval 0.95–1.00, and hazard ratio 0.94; 95% confidence interval 0.84–1.05, respectively).[20]

In another study, it is suggested lowered dialysate sodium levels for patients treated with both angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) because of the dual blockade of the renin-angiotensin system affects sodium balance.[21]

Several observational studies have demonstrated that lower DNa is related with less thirst[22,23], lower IDWG, lower ECF volume[24], and lower BP[25,26]; however, we could not discover research for elucidating its relationship with chronic inflammation in the literature.

But these beneficials results came along with disadvantageous of intradialytic symptoms such as hypotension and cramping.

The risk of mortality has been shown to be lower in patients with a dialysate sodium prescription >140 mEq/L (HR, 0.95 per 1 mEq/L higher; 95% CI, 0.93-0.97). However, the lower mortality observed in the adjusted analyzes in patients with dialyzed serum sodium levels <137 mEq/L versus dialysate sodium prescriptions >140 mEq/L is intriguing.[27]

In the late 1990s, CRP was accepted as a strong predictor of cardiovascular decease and entire mortality in HD and PD patients. Conventional assays for CRP are not sufficient sensitive to survey lower serum values associated with the inflammatory process. Therefore, the newer hs-CRP assays were started to use to measure serum CRP below 0.1 mg/L.

Hs-CRP may be utile for prognosticating coming mortality. In hemodialysis patients with a history of coronary artery disease, higher troponin levels were associated with higher mortality than in those without coronary disease. In patients without a history of coronary artery disease, hs-CRP levels >3 mg/L were associated with significantly higher mortality.[28]

In this present study we determined that the change in the DNa value of our patients with low-dose dialysate did not detect any statistically meaningful alteration in the serum hs-CRP values of the patients compared to the conventional dialysate. CRP is chosen as an inflammatory marker because it is more practical and reliable marker than other inflammatory indicators in clinical practice due to its relative consistency in serum, ease of acquisition, and appropriateness of the international standard.

### Limitations

We could not find any evidence that the DNa value may have an accurate influence on chronic inflammation in dialysis patients, independent of volume status, and a result to support low dialysate sodium hemodialysis in chronic hemodialysis patients with high exposure to chronic inflammation due to many factors, and any benefits that allow at the expense of hypotension, cramping, and thirst. The weaknesses of the study are the low number of patients, the short follow-up period, and the fact that the patients were not followed up for a sufficient period of time in terms of comorbid diseases, since only patients who had been on hemodialysis for the last 3 months were included in the study.

## CONCLUSION

In the light of this study, we suggest that the preference between the low and conventional dialysate sodium should be more related to the clinical consequences which may develop during or after dialysis session than its effect on chronic inflammation.

But we need further studies with larger patient populations and longer follow-up periods on the importance of dialysate sodium value in terms of chronic inflammation before saying the last word.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was conducted with the permission of the Ethics Committee of University of Health Sciences Trabzon Kanuni Training and Research Hospital (Date: 17.02.2017, Decision No: 23618724-000-2294).

### Informed Consent

All patients signed and free and informed consent form.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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